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High-fidelity measures of whole-brain functional connectivity and white matter integrity mediate relationships between TBI and PTSD symptoms

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Abstract

Traumatic brain injury (TBI) disrupts brain communication and increases risk for posttraumatic stress disorder (PTSD). However, mechanisms by which TBI-related disruption of brain communication confers PTSD risk have not been successfully elucidated in humans. This may be in part because functional magnetic resonance imaging (fMRI), the most common technique for measuring functional brain communication, is unreliable for characterizing individual patients. However, this unreliability can be overcome with sufficient within-individual data. Here, we examined whether relationships could be observed between TBI, structural and functional brain connectivity, and PTSD severity by collecting ~3.5 hours of resting-state fMRI and DTI data in each of 26 US military veterans. We observed that a TBI history was associated with decreased whole-brain resting-state functional connectivity (RSFC), while the number of lifetime TBIs was associated with reduced whole-brain fractional anisotropy (FA). Both RSFC and FA explained independent variance in PTSD severity, with RSFC mediating the TBI-PTSD relationship. Finally, we showed that large amounts of per-individual data produced highly reliable RSFC measures, and that relationships between TBI, RSFC/FA, and PTSD could not be observed with typical data quantities. These results demonstrate links between TBI, brain connectivity, and PTSD severity, and illustrate the need for precise characterization of individual patients using high-data fMRI scanning.

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Keywords

Traumatic Brain Injury; Posttraumatic Stress Disorder; White Matter Integrity; Functional Connectivity; High-data MRI

Introduction

Traumatic brain injury (TBI) is the signature wound of U.S. military personnel who fought in Iraq and Afghanistan ¹ and accounts for approximately 2.8 million emergency department visits, hospitalizations, and deaths in the civilian population in 2013 alone ². While mild TBI is associated primarily with immediate cognitive deficits that resolve without intervention ³⁻⁵, approximately 6–15% of patients experience persistent, long-term sequelae ⁶⁻¹⁰, including problems with learning and memory, anxiety and mood issues, and executive function deficits ¹¹⁻¹⁷. The common persistence of these symptoms means that over five million people are currently living with some form of TBI-induced disability ¹⁸.

When TBI-related symptoms persist, it is likely related to the presence of diffuse axonal injury, which is believed to be the most prevalent cause of TBI ^{19,20}. In this type of injury, the long-range axonal projections that connect distant regions of the brain are damaged by shearing forces induced by a head impact or blast wave. The prevalence of such axonal injuries in humans has been supported by a large number of in-vivo diffusion tensor imaging (DTI) MRI studies, which commonly find reduced integrity of many different large white matter tracts in TBI patients (reviewed in ^{21,22}).

The axonal fibers making up large white matter tracts represent the structural scaffolding used to convey neural impulses long distances between distributed, networked brain regions ^{23,24}. The brain does not function as a collection of brain regions independently processing information. Rather, cognition and behavior require the complex integration of multiple networked brain regions ²⁵. TBI-related damage to long-range axonal tracts likely impairs this networked communication. A growing body of work has used resting-state functional connectivity (RSFC) functional magnetic resonance imaging (fMRI) to demonstrate disrupted brain network communication in TBI ²⁶⁻⁴⁰. Such disrupted brain network communication is associated with cognitive and behavioral symptoms ^{28,34,41}. Together, these disruptions of structural and functional connectivity, and the resulting association with behavioral symptoms, suggest that TBI may be primarily conceptualized as a disorder of brain communication, in which diffuse axonal injuries disrupt networked communication between brain regions ^{22,42}.

A history of TBI is also strongly associated with the presence of Posttraumatic Stress Disorder (PTSD). The two diagnoses have many overlapping symptoms (e.g. insomnia, amnesia, concentration problems, irritability ⁴³), leading to apparent comorbidity in a large percentage of cases ⁴⁴⁻⁴⁷. The TBI-PTSD relationship appears to be even stronger in veterans, in whom a history of TBI can double or triple the risk of developing PTSD symptoms ^{48,49}. This increased risk for PTSD has been linked to the presence of persistent TBI-induced post-concussive symptoms ⁵⁰.

The neurobiological mechanisms by which TBI confers increased risk of PTSD are only beginning to be explored²². Conceptually, damage that alters the function of PTSD-relevant brain regions is likely to increase the risk of developing PTSD⁵¹. The primary neurological correlate of PTSD appears to be amygdala hyper-responsiveness coupled with reduced activity in ventromedial prefrontal cortex, suggesting reduced inhibitory control over amygdala and related medial temporal lobe structures^{52,53}. TBIs are likely to disrupt communication within emotion-regulation circuits⁵⁴; indeed, individuals with comorbid TBI/PTSD were shown to exhibit a particularly severe decoupling of prefrontal cortex and hippocampus⁵⁵. In practice, however, PTSD symptoms have been associated with altered function in many brain regions, including cortical networks in medial and lateral parietal and prefrontal cortex that may influence amygdala/ventromedial prefrontal cortex function⁵⁶. There is a need to establish explicit links between 1) TBI, 2) structural brain damage / functional brain impairment across many networked regions, and 3) PTSD symptoms⁵⁷.

One reason such links have been elusive may be that MRI- and especially fMRI-based measures are relatively noisy⁵⁸, and so may be unreliable for characterizing brain function in individuals with a high degree of precision. This limitation is particularly problematic for the TBI population, in which white matter damage^{59–62} and network disruption^{26,29,33} are known to be diffuse and variable, because brain-behavior relationships cannot be accurately described within a variable population if the brain metric is unstable. Importantly, recent work has shown that stable measures of brain function can be achieved if a sufficient quantity of MRI data is collected^{63–66}.

In the present study, we collected large quantities of DTI and fMRI data in 26 US Military veterans. We first verified that reliable measures of white matter integrity and RSFC strength could be obtained with these large data quantities. We then examined relationships between TBI history, whole-brain white matter integrity, whole-brain RSFC strength, and PTSD symptom severity. Our analysis was organized around the overarching idea that direct effects of TBIs on PTSD symptom severity are likely to be mediated by their effects on white matter damage and brain network communication. We specifically hypothesized that 1) a history of TBI would be related to reduced white matter integrity across the whole brain; 2) a history of TBI would be related to reduced RSFC strength across the whole brain, and this effect would be mediated by white matter integrity; and 3) a history of TBI would be associated with increased PTSD symptom severity, and this effect would be mediated by white matter integrity and RSFC. A graphical summary of this conceptual framework can be seen in Figure 1.

Materials and Methods

Subjects

Data were collected from 37 US Military Veterans recruited from the areas surrounding Waco, TX. Before beginning the study, participants were screened and excluded for MRI safety issues, any Axis I psychotic disorder, bipolar disorder, dementia, substance abuse disorder, or any substance use in the last 12 hours before MRI scanning. Informed consent was obtained from all participants. This study was approved by the Central Texas Veterans Health Care System Institutional Review Board.

Each participant completed between one and five two-hour study sessions on separate days spanning less than three months. The first session included participant screening, informed consent, behavioral assessment, neuropsychological testing (not described here), and a brief initial MRI scanning session to determine whether participants could tolerate the scanning environment without excessive movement.

Participants who exhibited motion in fewer than 50% of timepoints in the initial fMRI scan (see “fMRI Preprocessing” below for details) were invited back for up to four additional sessions. These additional sessions were devoted entirely to MRI scanning. In all scanning sessions, the MRI technologist performing the scanning was blind to the goals of the study and to the TBI/PTSD status of the participant.

In total, 27 participants completed the initial session and at least one scanning-only session. One participant was subsequently excluded from analyses due to outlier measures of functional connectivity believed to result from a scanner malfunction. This left 26 participants (5 females; mean \pm SD age: 37.0 \pm 11.8) included in the current results.

Behavioral assessment

Behavioral assessment focused on determining whether individuals had a history of TBI, as well as identifying the presence and severity of PTSD symptoms. TBI history was assessed using the Vasterling TBI assessment interview⁶⁷, which obtains self-reports of all lifetime TBI events. Measures of interest in this study included the severity of the worst TBI event, as well as the total number of lifetime TBI events. We found that 5 participants had no history of TBI, while 17 had at least one mild TBI (but no moderate or severe TBIs) and 4 had at least one moderate TBI (but no severe TBIs). No individuals with a history of severe TBI completed the scanning protocol. The mean \pm SD number of lifetime TBI events experienced was 2.1 \pm 1.7 (range: 0 – 6). The time since the most recent TBI was also recorded.

The severity of PTSD symptoms was assessed using the PTSD Check List for DSM-5 (PCL-5)⁶⁸. The measure of interest was the summed PCL-5 symptom severity score. PCL-5 scores were not available for one participant; that participant was thus excluded from all analyses examining relationships with PCL-5. The mean \pm SD PCL-5 score of the remaining participants was 34.2 \pm 22.7 (range: 0 – 77).

We also assessed combat exposure using the 34-item version of the Full Combat Exposure Scale (FCES;⁶⁹), in which participants rate the frequency of their exposure to a variety of combat elements. FCES scores have previously been associated with PTSD severity⁷⁰. Finally, we recorded the medications currently taken by each subject and grouped them into major medication categories. None of these measures except PCL-5 score differed between the TBI groups (Table 1).

MRI image acquisition

Imaging was performed on a Philips Achieva 3T MRI scanner. Scanning in the initial session included collection of one T1-weighted MPRAGE image, one DTI scan, and one T2*-weighted BOLD contrast sensitive fMRI scan. fMRI was collected during the “resting

state”, in which participants passively viewed a white crosshair on a black background and were instructed not to fall asleep.

Scanning in subsequent sessions included collection of one MPRAGE, one DTI scan, and as many 6.6-minute resting state fMRI scans as could be collected in the rest of the two-hour session. Participants took breaks after every thirty minutes of scanning and were encouraged to request additional breaks whenever they felt fatigued. Breaks were allowed to be of any length but were generally around five minutes.

Scanning parameters were as follows:

T1-weighted sagittal MP-RAGE —TE = 3.08 ms, TR partition = 2.4 s, TI = 1,000 ms, flip angle = 8 degrees, 176 slices, 1x1x1 mm voxels.

DTI — 32 directions with two b-values ($b=0 \text{ sec/mm}^2$ and $b = 800 \text{ sec/mm}^2$), TE = 93 ms, TR = 3891 ms, AP phase encoding, flip angle = 90 degrees, in-plane resolution = 2x2 mm, 60 slices, slice thickness = 2 mm.

fMRI — a gradient echo-planar imaging sequence with TE = 30 ms, flip angle = 90 degrees, in-plane resolution = 3x3 mm, 34 3.0mm-thick axial slices with a 1.0mm gap between slices, TR=3.0s, 132 volumes acquired per run for 6 minutes and 36 seconds of scan time.

Across all scanning sessions, participants underwent an average \pm SD of 4.5 ± 1.2 DTI scans (range: 2 to 6) and an average \pm SD of 24.9 ± 10.1 6.6-minute resting state scans (range: 5 to 44).

MRI Processing and Analysis

Structural MRI data

T1 preprocessing: All T1-weighted MPRAGE images were visually inspected for image quality and for potential abnormalities. The best image from each subject was corrected for magnetic field bias, skull-stripped, and linearly warped to the MNI-152 template using FSL tools ⁷¹.

Cortical surface generation: Generation of cortical surfaces from the MPRAGE followed procedures described in ⁷². Anatomical surfaces were generated from the native-space MPRAGE using FreeSurfer’s recon-all processing pipeline (version 5.3) ^{73–76}. The fsaverage-registered left and right hemisphere surfaces were brought into register with each other, resampled to 164,000 vertices using Caret tools ⁷⁷, and down-sampled to the fs_LR 32k template space. These surfaces were then transformed into MNI atlas volumetric space by applying the previously calculated MPRAGE-to-MNI transformation.

Diffusion MRI data

DTI Processing: DTI images were processed using the Diffusion Toolbox in FSL ^{71,78}. All diffusion tensor images were corrected for eddy currents. In each image, a diffusion tensor model was fitted and used to calculate fractional anisotropy (FA) in each voxel. A linear

rigid-body registration was computed between each B0 image and the native-space MPRAGE image, concatenated with the MPRAGE-to-MNI transformation and an interpolation into 2-mm isotropic space, and applied to the FA image. The resulting MNI-space FA images were then averaged across DTI runs for each individual (see Figure 2A).

White matter integrity calculation: For each subject, we calculated mean FA across all of the canonical white matter tracts in the Johns Hopkins University white matter tract atlas⁷⁹, masked by each individual subject's white matter segmentation. This atlas includes 48 discrete tracts; our DTI scans provided coverage for 38 of these tracts (the remainder being in the brainstem). We also calculated mean FA in each of these specific tracts.

Functional MRI data

fMRI preprocessing: Functional data were preprocessed using FSL tools and in-house Matlab scripts. All runs underwent correction of slice timing effects and calculation of within-run correction for head movement. Linear rigid-body registrations were calculated from each run to the most representative run (calculated as the run with maximal spatial correlation to all other runs). A linear warp was calculated from the most representative mean image to the native volumetric MPRAGE using the boundary-based registration method⁸⁰. These within-run, across-run, representative run-to-MPRAGE, and MPRAGE-to-MNI transformations were concatenated with an interpolation into 3-mm isotropic space and applied to each volume. The resulting MNI-space fMRI runs were intensity-normalized to a whole brain mode value of 1000.

Additional preprocessing steps to reduce spurious variance were executed as recommended in^{81,82}. First, temporal masks were created to flag and censor motion-contaminated frames. Motion contaminated volumes were identified by frame-by-frame displacement (FD, described in⁸³). Several subjects had a high-frequency artifact in the motion estimates, primarily in the phase encode direction, that did not appear to reflect biological movement. Similar effects have previously been observed in data from the Human Connectome Project^{84,85}. We thus filtered the FD timecourses to retain effects occurring below 0.1 Hz. Frames with filtered FD > .04mm were flagged as motion-contaminated, following⁷⁶. Across all subjects, these masks censored $23.7\% \pm 17.9\%$ (range: 1.5% – 66.8%) of the data; on average, subjects retained 2420 ± 1174 volumes (range: 515 – 4943). Neither the percent of data lost nor the total number of frames retained differed by TBI status (Table 1).

After computing these temporal masks, data were processed with the following steps: (i) demeaning and detrending; (ii) concatenation across runs; (iii), multiple regression of nuisance signals including: whole brain signal, white matter signal, top principal components explaining 75% of the variance in ventricular signal, run identity, session identity, and motion regressors derived by Volterra expansion⁸⁶, with censored data ignored during beta estimation; (iv) interpolation across censored frames^{83,87}; and (v) band-pass filtering ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$). Censored frames were then excised for all subsequent analyses.

To visually assess noise levels in the fMRI data, and to assess the efficacy of the motion censoring and nuisance regression procedures, we constructed “grayplots” of this data,

following⁸⁴. Briefly, signal strength at every timepoint was calculated from a random sample of voxels within the cortical gray matter ribbon, both before and after motion censoring/nuisance regression. These strengths were plotted as a time x voxels matrix for each subject and visually examined for evidence of global artifact. This examination revealed that all subjects exhibited large global signal fluctuations which were effectively eliminated by the motion censoring and nuisance regression procedures (see Supplemental Figures 1–3).

The fMRI volumetric timeseries were then sampled to each subject's left and right-hemisphere cortical surfaces using the ribbon-constrained sampling procedure⁸⁸ in Connectome Workbench 1.0⁷². Surface-space timecourses were deformed and resampled to the 32k fs_LR surface. This surface data was combined with volumetric subcortical gray matter and cerebellar data into the CIFTI format. Finally, the resting-state timecourses were smoothed with geodesic 2D (for surface data) and Euclidean 3D (for volumetric data) Gaussian kernels (FWHM = 6mm).

Resting state functional connectivity calculation: To evaluate RSFC between brain regions, we employed a previously-published parcellation of human cortex⁸⁹. For each subject, cortical vertex timecourses were averaged within each parcel to produce a parcel average timecourse. Connectivity relationships between parcels were calculated by cross-correlating the timecourses of all parcels against each other; the resulting correlation values were Fisher Z-transformed to improve normality. This resulted in a parcel x parcel connectivity matrix of Z(r) values for each subject (see Figure 2D for an example).

These parcels are known to be organized into 14 discrete networks (Figure 2C). RSFC within these networks is most likely to represent networked area-to-area brain communication. To obtain a summary RSFC measure of these strong within-network functional connections, we calculated the average functional connectivity across all within-network parcel-to-parcel connections (Figure 2E), excluding all parcels in low-signal regions (ventral temporal and orbitofrontal cortex) that do not have known network identities (gray areas in Figure 2C).

Notably, neither the whole-brain FA nor the within-network RSFC measures appeared to be influenced by potential residual (uncontrolled) effects of in-scanner motion, as neither the percent of frames lost to motion nor the average FD in retained frames was associated with either measure (all p s > .15; Supplemental Figure 4).

Reliability of FA and RSFC measures

We examined how collection of increasing amounts of data improved the within-subject reliability of FA and RSFC measures. This approach followed the iterative split-half reliability analyses described in^{63,65}.

FA: For each subject, the DTI sessions were randomly split into two approximately equal subsets of sessions. Mean FA values were calculated in each of the 38 a priori tracts (see above) using all data in one of the subsets (the smaller subset, if the total number of sessions was odd). A varying number of sessions (1–3, when possible) was randomly selected from

the other subset, and mean FA values were calculated in each of the a priori tracts using this data. The split-data similarity of FA values was calculated as the correlation of tract FA values in the two data subsets. This procedure was repeated in each subject for all possible combinatorial iterations of sessions.

RSFC: For each subject, the RSFC sessions were randomly split into two equal subsets of sessions. A parcel-to-parcel connectivity matrix (see above) was calculated from all data in one of the data subsets (the smaller subset, if the total number of sessions was odd). A varying amount of data (ranging from 2.5 minutes to 100 minutes after motion censoring, when possible) was randomly selected from the other subset. This data was contiguous within sessions but did not necessarily include temporally adjacent sessions. A connectivity matrix was calculated for this data. The similarity of the matrices from the two subsets was calculated as the correlation of $Z(r)$ values in the upper triangle of the matrices. To obtain robust estimates of this split-half similarity, this procedure was iterated 1000 times for each subject and for each quantity of data tested, with a different random selection of data in each iteration.

Statistical analysis of relationships between TBI, whole-brain white matter integrity, whole-brain functional connectivity, and PTSD

We examined 1) whether TBI is related to FA; 2) whether TBI is related to RSFC, and whether that relationship is mediated by effects of FA; and 3) whether TBI is related to PTSD symptoms, and whether that effect is mediated by effects of FA and/or RSFC. To accomplish this, we conducted the following statistical tests (all 2-tailed, with significance criterion set at $p < .05$):

TBI vs PTSD: We used a one-way ANOVA and a Pearson's correlation, respectively, to test whether TBI status—i.e., the severity of the worst TBI event reported (none, mild, moderate)—or the total number of lifetime TBIs (in individuals with at least one TBI) is related to PCL-5 score.

TBI vs FA: We used a one-way ANOVA and a Pearson's correlation, respectively, to test whether TBI status or number of lifetime TBIs is related to mean FA values across all white matter tracts.

TBI vs RSFC: We used a one-way ANOVA and a Pearson's correlation, respectively, to test whether TBI status or number of lifetime TBIs influenced mean RSFC strength.

FA vs RSFC, and mediation effects of FA on TBI-RSFC relationships: We conducted a Pearson correlation to test whether mean FA was associated with mean RSFC strength. We then conducted an ANCOVA and a partial correlation to test how TBI status and number, respectively, are related to RSFC when accounting for FA.

FA/RSFC vs PTSD, and mediation effects of FA/RSFC on TBI-PTSD relationships: We conducted Pearson's correlations to test whether mean FA and/or mean RSFC strength were each associated with PCL-5 scores, as well as a multiple regression to test whether they were associated with PCL-5 scores in combination. For each significant

relationship between TBI-FA/RSFC and between FA/RSFC and PCL-5, we conducted an ANCOVA/partial correlation (as appropriate) testing how TBI status/number is related to PCL-5 when accounting for FA/RSFC.

Results

Reliability of DTI data is very high after only a few scans, but RSFC requires large amounts of data to achieve high reliability.

Average within-tract FA values were highly similar across split portions of the data, indicating high reliability of the FA measure (Figure 3A). When calculating FA from only one DTI scan, all subjects exhibited an average correlation of at least $r=.92$ between single scans and an average of multiple (2–3) separate scans. Indeed, for the majority of subjects (21/26), this correlation was between $r=.97$ and $r=.995$. Increasing the number of DTI scans included did increase this split-half similarity, though only marginally, as could be expected for a near-ceiling measure.

By contrast, RSFC correlation matrices were much less similar when comparing split halves of data to a small quantity of data (similar to the quantity used in many other studies), indicating relatively low reliability (Figure 3B). When calculating RSFC values from only 2.5 minutes of (post motion-censoring) data, subjects exhibited an average correlation of only $r=.54$ to the split half. This value rose to $r=.83$ when RSFC values were calculated using 20 minutes of data, and to $r=.91$ when values were calculated using an hour of data. This suggests that RSFC values are not highly reliable unless a relatively large quantity of data (after motion censoring) is included in the calculation. As noted above, all subjects in this study had at least 26 minutes of data available for RSFC calculation.

In post-hoc analyses, we also characterized these reliabilities as the average (i.e., expected) differences between split portions of data, iterated across many data splits, for the whole-brain FA and within-network RSFC measures. The results mirror the above reliability findings (See Supplemental Figure 5). For whole-brain FA, expected differences were quite low: $FA \sim .007$ for one DTI session, decreasing only slightly to $\sim .005$ with additional data collection. For within-network RSFC, $RSFC \sim .035$ for one fMRI session, decreasing substantially to $\sim .015$ with additional data. Notably, with sufficient data, these expected differences were substantially smaller than the scale of the TBI-DTI relationship or the magnitude of RSFC differences between TBI groups (see below).

Complex relationships exist between TBI, whole-brain white matter integrity, whole-brain functional connectivity, and PTSD symptoms.

TBI status, but not number, is related to PTSD symptom severity.—We tested whether total score on the PTSD Check List (PCL-5) differed between groups with varying TBI status, taken from the severity of the worst lifetime TBI event (none/mild/moderate). We found that TBI status was related to PCL-5 score ($F(2,23) = 3.4, p = .05$; Figure 4A). This effect appeared to be driven by parametric effects of TBI status on PCL-5 scores. Post-hoc two-sample t-tests indicated that PCL-5 scores were significantly lower in the No TBI group than in the Moderate TBI group ($t(6) = 3.18, p = .02$), while differences between the

Mild TBI group and the other two groups were both at trend level (No TBI vs Mild TBI: $t(19)=1.70$, $p=.10$; Mild TBI vs Moderate TBI: $t(17) = 1.69$, $p=.10$).

By contrast, the total number of lifetime TBI events was not related to PCL-5 scores, either alone ($r(24)=-.14$, $p=.55$; Figure 4B) or when controlling for TBI status (partial $r(23) = -.11$, $p = .60$).

TBI number, but not status, is related to white matter integrity.—We tested whether the severity of the worst lifetime TBI event is related to average FA values within all a priori white matter tracts. We observed no relationship between TBI status and average FA ($F(2,23) = .70$, $p = .51$; Figure 4C). Exploratory tests examining each a priori tract separately also revealed no significant effects of TBI status on FA values (all uncorrected $p > .08$).

However, when examined in individuals with at least one TBI, a larger total number of lifetime TBI events was related to lower FA values ($r(20) = -.53$, $p = .01$; Figure 4D). This effect held when controlling for TBI status in all subjects (partial $r(19) = -.51$, $p = .01$).

TBI presence, but not number, is related to reduced RSFC strength within networks.—We tested whether the severity of the worst lifetime TBI event is related to RSFC strength within a priori networks. We observed that TBI status is related to RSFC strength within networks ($F(2,23)=8.00$, $p = .002$; Figure 4E). Post-hoc t-tests determined that this effect was driven by the individuals with no history of TBI exhibiting significantly stronger RSFC than individuals with a TBI history (No TBI vs Mild TBI: $t(20) = 3.69$, $p=.002$; No TBI vs Moderate TBI: $t(7) = 3.19$, $p=.02$). However, RSFC strength did not differ between individuals with a mild TBI history and those with a moderate TBI history ($t(19) = .01$, $p = .99$), indicating that RSFC is decreased in individuals with any history of TBI, regardless of severity.

By contrast, TBI number was not related to RSFC strength either alone ($r(20) = .21$, $p = .36$; Figure 4F), or when controlling for TBI status (partial $r(19) = .18$, $p = .39$).

White matter integrity is not related to RSFC strength.—We tested whether average FA values across all white matter tracts were related to RSFC strength within networks. We found no significant association between these measures ($r(25) = -.22$, $p = .27$).

Reduced RSFC strength is associated with increased PTSD symptom severity.—We examined whether RSFC strength within networks was related to PCL-5 scores. We found that weaker RSFC connections were associated with increased PCL-5 scores ($r(24) = -.47$, $p = .02$; Figure 5B). This effect remained significant at trend level when excluding one participant who had the lowest RSFC strength and the highest PCL-5 score ($r(23) = -.35$, $p = .09$).

RSFC strength mediates relationships between TBI status and PTSD.—We examined whether the strength of within-network RSFC connections mediates the

relationship between TBI status and PCL-5 scores. We found that including RSFC strength as a covariate reduced the TBI status-PCL relationship to nonsignificance ($F(2,21) = 1.45$, $p = .25$), indicating that within-network RSFC mediates the effect of TBI status on PTSD symptoms.

Reduced white matter integrity is related to increased PTSD symptom severity in combination with RSFC strength.—We tested whether average FA values within white matter tracts were associated with total PCL-5 score. We found that FA values did not significantly correlate with PCL-5 scores ($r(24) = -.21$, $p = .29$; Figure 5A). However, when FA values and within-network RSFC strength were both entered as factors of interest explaining PCL-5 scores, we found that both were significant (FA: $F(1,22) = 4.13$, partial $r(23) = -.40$, $p = .05$, Figure 5C ; RSFC: $F(1,22) = 9.47$, partial $r(23) = -.55$, $p = .005$, Figure 5D), together explaining 41% of the total variance in PCL-5 scores. This indicates that white matter integrity is related to PTSD symptom severity only after controlling for differences in functional connectivity.

Notably, while the integrity of the link between the ventromedial prefrontal cortex and the amygdala nucleus is thought to be a key factor in risk for developing PTSD, the present effects were not strongly driven by these connections (see Supplementary Materials).

Observation of relationships between TBI, white matter integrity, functional connectivity, and PTSD symptoms require large amounts of data

We examined whether observation of relationships between TBI, brain connectivity, and PTSD severity requires collection of large quantities of data. All RSFC measures were recalculated using only the first ten minutes of fMRI data collected, and all FA measures were recalculated using only the first DTI scanning session. These quantities represent the typical amounts of data that are collected in the literature. We then tested whether the relationships between TBI status/number, within-network RSFC, FA, and PTSD symptom severity could still be observed when employing these quantities of data.

We found that when we used these less-reliable measures, within-network RSFC strength no longer differed by TBI status ($F(2,25)=2.29$, $p=.12$) or correlated with PCL scores ($r(24) = -.22$, $p=.28$). FA values still correlated with the number of TBI events suffered ($r(20) = -.51$, $p = .02$), but FA values were no longer associated with PCL scores in combination with RSFC strength ($F(1,22)=1.40$, $p=.25$).

Relationships among TBI, whole-brain white matter integrity, whole-brain functional connectivity, and PTSD severity are not driven by the integrity of the amygdala-ventromedial prefrontal cortex link.

The integrity of the link between the ventromedial prefrontal cortex and the amygdala nucleus is thought to be a key factor in risk for developing PTSD. In post-hoc tests, we examined whether the relationships observed above between whole-brain FA / whole-brain RSFC were driven by FA within the uncinate fasciculus and/or RSFC between the amygdala and ventromedial prefrontal cortex. We found no significant relationship between mean FA in the bilateral uncinate fasciculus and PCL-5 scores ($r(24) = -.05$, $p = .81$). We also found

no relationship between bilateral amygdala to bilateral vmPFC RSFC and PCL-5 scores ($r(24) = -.23$, $p = .27$), and no significant relationships when both uncinate FA and amygdala-vmPFC RSFC were entered into the same model explaining PCL-5 scores ($ps > .25$). Further, we found that whole-brain FC still significantly explained variance in PCL-5 ($p=.008$), and whole-brain FA still explained PCL-5 at trend-level ($p = .065$), after controlling for uncinate FA and amygdala-vmPFC FC (which did not explain PCL-5 variance in this model, $ps > .35$). This indicates that the observed relationships between whole-brain FA, RSFC, and PCL-5 scores were not driven by the link between ventromedial prefrontal cortex and amygdala.

Notably, the lack of observed association between PCL-5 scores and amygdala-vmPFC connectivity may be influenced by signal loss in these specific regions, which could result in reduced reliability of these FA and RSFC measures relative to the rest of the brain (as shown in ⁶⁶). A post-hoc reliability analysis (Supplemental Figure 6) examined the stability of these connection-specific measures in the same fashion as the whole-brain analysis shown in Supplemental Figure 5. This analysis suggested that reliability of uncinate fasciculus FA (expected FA $\sim = .01$) was moderately worse than the reliability of whole-brain FA (expected FA $\sim = .005$). However, the reliability of the amygdala-vmPFC RSFC measure (expected RSFC $\sim = .07$) was substantially worse than the reliability of the whole-brain within-network RSFC measure (expected RSFC $\sim = .015$), even with large amounts of data. Thus, the lack of association observed here should not be treated as a definitive negative result.

Discussion

Although there is a clear relationship between TBI and PTSD, exploration of mechanisms by which TBI affects PTSD symptomology is in its early stages²². TBI seems to increase the likelihood of developing PTSD ^{48,49}, even when controlling for mechanism of injury ⁹⁰. This suggests that the brain alterations induced by TBI can act as a permissive “gateway” that induces a biological vulnerability to the development of PTSD (and other neuropsychiatric syndromes) ^{91,92}. The neural mechanism behind this “gateway” effect has been hypothesized to be related to damage suffered in neural connections that enable the control or suppression of intrusive emotions and memories ^{22,51}, but such a mechanism has not clearly been demonstrated. Here we demonstrate potential mechanistic links between TBI, brain connectivity, and PTSD severity (see Figure 6 for graphical summary).

We identified these links between TBI, brain connectivity, and PTSD in a sample with very large amounts of per-individual MRI data, allowing elucidation of relationships that, as we demonstrate, could not be observed with more typical per-individual data quantities. While our relatively small sample size can be considered a weakness of the study, the dramatic increase in reliability of the RSFC data gained by collecting large amounts of data (Figure 3B) is a considerable strength and makes the dataset unique. Previous work has argued that results obtained using small quantities of per-subject fMRI data (5–20 minutes) cannot precisely characterize brain function and organization ^{63–66}. Here we demonstrate that this principle also holds in a TBI population. As RSFC reliability depends critically on the amount of data collected, the RSFC estimates obtained here are more accurate than those

obtained in any previous work examining RSFC in TBI or PTSD, which permitted observation of effects that could not be seen if tested with low-data versions of this measure. Notably, while estimates of FA did not require multiple DTI scanning sessions to obtain high reliability (Figure 3A), such estimates did not explain PTSD symptom severity unless controlling for the (highly reliable) measures of RSFC strength. This work thus illustrates the need for precise characterization of individual patients using high-data fMRI scanning in order to accurately elucidate relationships between TBI/PTSD and brain function.

We found not one but two dissociable pathways by which brain alterations mediated TBI effects on PTSD severity. First, we observed that the presence of TBI is associated with increased PTSD symptom severity, and this effect was mediated by decreases in whole-brain RSFC. While RSFC is known to be reduced across many network connections in individuals with a history of TBI^{26,29,33,35,36,39} and is known to be associated with PTSD symptom severity⁹³⁻⁹⁷, the present findings represent the first explicit linkage of these two effects. Interestingly, the locations of specific functional connections disrupted in TBI or contributing to PTSD severity have been inconsistent across these previous studies, ranging from amygdala^{93,94,96} to hippocampus^{96,97} to somatomotor regions³⁶ to regions of the Default network (medial prefrontal and parietal cortex, and angular gyrus)^{33,35,93,95-97} to widespread disruption across many cortical networks^{26,29,39}. The present findings support the idea that TBI-related disruptions in RSFC are indeed widespread, and that such whole-brain disruptions contribute to PTSD symptoms.

Second, we observed that the number of TBIs suffered was unrelated to PTSD severity, but it was associated with reduced whole-brain white matter integrity, which in turn was associated with PTSD severity after controlling for RSFC. While it is well established that TBIs reduce white matter tract integrity^{21,22}, explicit links between these TBI-induced white matter alterations and PTSD severity have been difficult to demonstrate⁹⁸⁻¹⁰⁰. The present results suggest a possible explanation for this difficulty: we observed that TBI-induced FA reductions were associated with PTSD symptom severity only after controlling for reductions in RSFC strength, which has not been attempted in previous work.

Our a priori model (Figure 1) predicted that TBI would be associated with FA decreases, which would result in reduced RSFC, which in turn would increase PTSD severity. This model rested on the idea that disruptions in white matter integrity would impair functional connectivity. Surprisingly, we found no positive relationship between FA and RSFC. While it is possible that these measures truly are linked, and that our failure to observe the relationship was due to inaccurate measurement, we think this explanation is unlikely, for several reasons. First, our high-data protocol resulted in highly reliable measures of both FA and RSFC (Figure 3). Second, these measures were both associated with (separate) metrics of TBI, and were both behaviorally relevant, explaining independent variance in PTSD symptom severity. Third, while the existence of an FA-RSFC relationship is generally assumed, results of previous work that has actually examined this relationship have been inconsistent. While^{101,102} demonstrated the expected positive relationships between FA and RSFC in specific Default network tracts,¹⁰³ demonstrated negative relationships between FA and RSFC in hippocampal-related connections, and both¹⁰⁴ and¹⁰⁵ failed to demonstrate significant FA-RSFC associations.

The present results suggest not only that reliable FA and RSFC estimates are uncorrelated at the whole brain level, but that they reflect partially separable biological factors that explain independent variance in PTSD severity and, importantly, are associated with different aspects of TBI. Reductions in FA were correlated with the number of TBIs suffered by participants, while reductions in RSFC were associated with the presence of any TBI history. While the biological mechanisms behind this distinction are not yet clear, one potential explanation is that RSFC strength may be primarily indexing the integrity of local interneuron connections within the cortex (as the fMRI BOLD signal is known to correspond primarily to local processing rather than pyramidal spiking activity; ^{106,107}), which may be sensitive to single insults. The tract-restricted FA calculated here, by contrast, reflects the integrity of robust white matter tracts in the center of the brain, which may be more continually degraded by multiple insults. Further research is needed to investigate this speculation.

It is notable that PTSD severity was associated with whole-brain FA and RSFC, but not correlated with uncinate FA or amygdala-vmPFC RSFC. In the absence of TBI, alterations in structural ¹⁰⁸ and functional ^{109,110} connectivity between the amygdala and the mPFC have been previously associated with PTSD, and are posited to reflect impairments in the top-down regulation of amygdala responses. It is possible that the presence of TBI may alter this relationship, potentially due to post-traumatic amnesia following the injury preventing the encoding of fearful aspects of the trauma into memory in the first place ⁵¹. However, it is also plausible that these relationships could be not observed because, unlike the whole-brain measures, the specific reliability of the uncinate FA and (especially) the amygdala-vmPFC RSFC measures were relatively poor (Supplemental Figure 6) and may have been insufficient to obtain truly accurate individual estimates. This finding follows recent work suggesting that subcortical RSFC measures may be particularly unreliable ⁶⁶. Cortical RSFC measures may be more promising for examination of patient-specific effects related to PTSD.

Limitations

As noted above, this work employs measures of brain structure and especially function that are almost certainly more reliable than those used in any previous work. While the precision of these measurements can help mitigate the problems with the small sample size employed here, they cannot eliminate it entirely. In particular, the No TBI and Moderate TBI groups had very small samples. As such, these findings must be considered preliminary, requiring replication and expansion using similar high-data protocols for reliable characterization of individuals.

It should also be noted that the technical quality of these scans, while relatively standard in the field, was not at the cutting edge. In particular, the quality of the diffusion imaging could be improved with higher spatial and angular resolution imaging, while the quality of the functional imaging could potentially be improved with the use of multiband imaging allowing higher spatial and temporal resolution, resulting in greater specificity of effects. However, such improvements in resolution usually come at the cost of reduced signal to noise ratio (e.g., ¹¹¹), which would potentially reduce the reliability of individual-specific

FA or RSFC measures. Further work should be done to determine scanning parameters that may result in an optimal combination of effect specificity and measure reliability at the individual level. Additional improvements in FA measures could also be gained by the correction of vibration artifacts using a phase-reversed image ¹¹², which should be incorporated in future work exploring these effects.

The T1 scans obtained here were visually inspected for the presence of abnormality and potential neuropathology relating to TBI. However, a more sensitive check for such pathology could be conducted using SWI or FLAIR images. While such images are not strictly diagnostic of TBI, and in particular often fail to detect mild TBI ¹¹³, identification of neuropathology using these modalities in individual patients has the potential to interface very well with the highly reliable, patient-specific DTI and fMRI measures obtained using this approach. Future work will test whether the presence of such pathology may predict impairments in structural or functional connectivity above and beyond a history of TBI, as well as whether it may combine with the connectivity measures to predict particularly severe PTSD symptoms or behavioral outcomes.

Notably, recent work has suggested that exposure to a blast may particularly alter measures of white matter integrity ^{59,62,98} and functional connectivity ^{31,114,115} above and beyond impact-related TBI, though it is not clear that blast exposure results in differential symptoms or outcomes ¹¹⁶. While our sample size precluded the ability to test for blast-specific effects in this work, future work should focus on examining how blast exposure may influence relationships between TBI, brain connectivity, and PTSD severity.

This work focuses on biological factors resulting from TBI that influence PTSD symptom severity. However, psychological factors stemming from traumatic experiences also influence PTSD ^{117,118}. Here, level of combat exposure (commonly including traumatic events) did not differ statistically between TBI groups (though numeric differences were apparent; Table 1). While we do not think that different levels of trauma exposure between groups explain the complex TBI-connectivity-PTSD effects observed here, trauma exposure does likely influence brain function independently of TBI-induced damage by driving activity/plasticity in emotion regulation circuits ^{119–121}. A full examination of potential interactions among TBI injury severity, exposure to psychological trauma, measures of brain function, and PTSD symptoms is needed in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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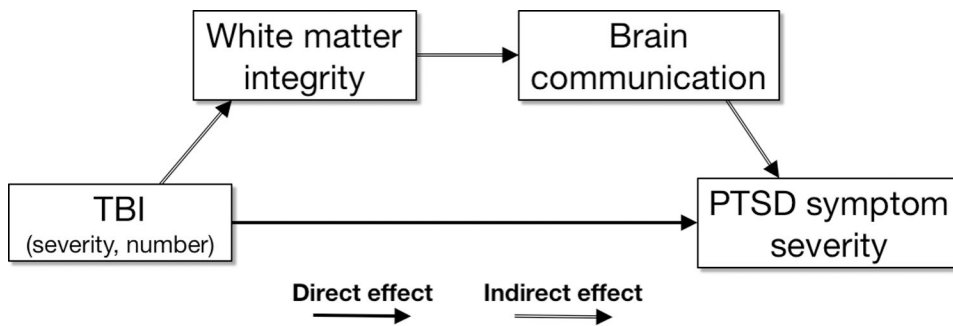


Figure 1: Hypothesized model for how TBI increases risk for PTSD symptoms by altering brain structure and function.

In this framework, direct effects of TBI on PTSD severity (dotted line) are mediated by indirect effects of TBI on white matter integrity, which reduce brain communication, which in turn increase PTSD symptoms.

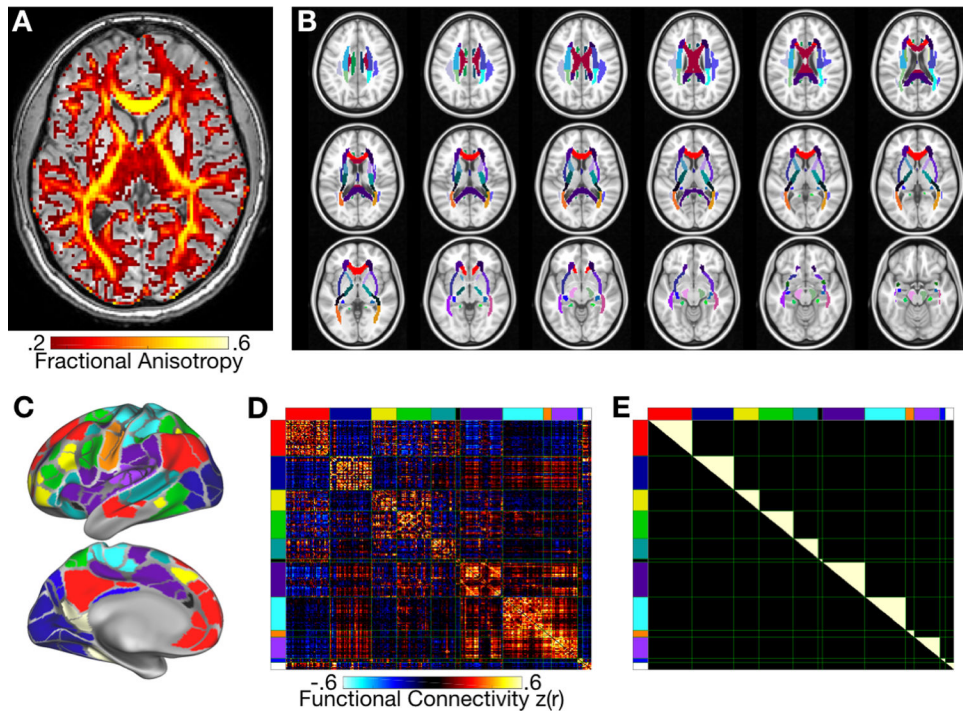


Figure 2: Data collected in the present study.

A: Diffusion Tensor Imaging scans were collected in order to produce maps of Fractional Anisotropy (FA), a measure of white matter integrity. An FA map is shown for one example subject. **B:** FA was assessed in each of many different a priori white matter tracts. Each tract is shown in a different color. **C:** Resting-state fMRI scans were collected, and data were averaged within each of 333 a priori parcels on the cortex. **D:** Temporal correlations were computed between all parcel timecourses to produce a functional connectivity value between each pair of parcels. A matrix illustrating the strength of functional connectivity between each parcel pair is shown for a single subject. The matrix is ordered by the known network organization of this parcel set (compare colored blocks on axes to parcel colors in C). **E:** For each subject, functional connectivity values from D were averaged across all unique within-network connections, as illustrated here in white.

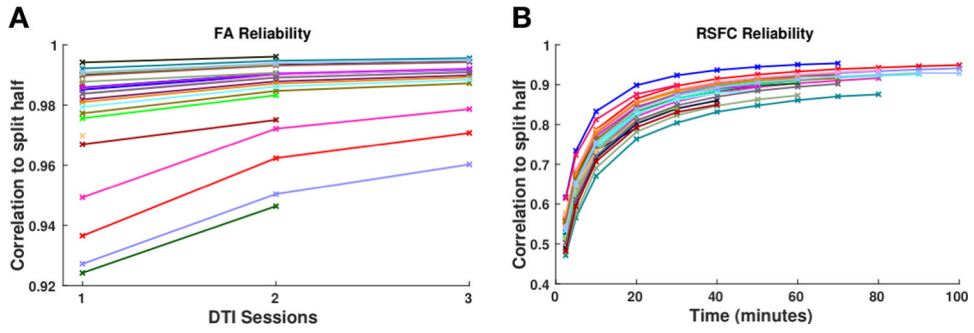


Figure 3: Split-data reliability of FA and RSFC measures increases with the amount of data collected.

A: Tract-wise FA measures computed from a given number of sessions (x-axis) was randomly selected and correlated against measures from an independent sample of half of the DTI sessions. This was repeated for all unique combinations of sessions. **B:** RSFC matrices computed from a given amount of motion-censored data (x-axis) was randomly selected and compared to a random independent sample of half of the resting-state scans; this was repeated 1000 times. Lines represent unique subjects.

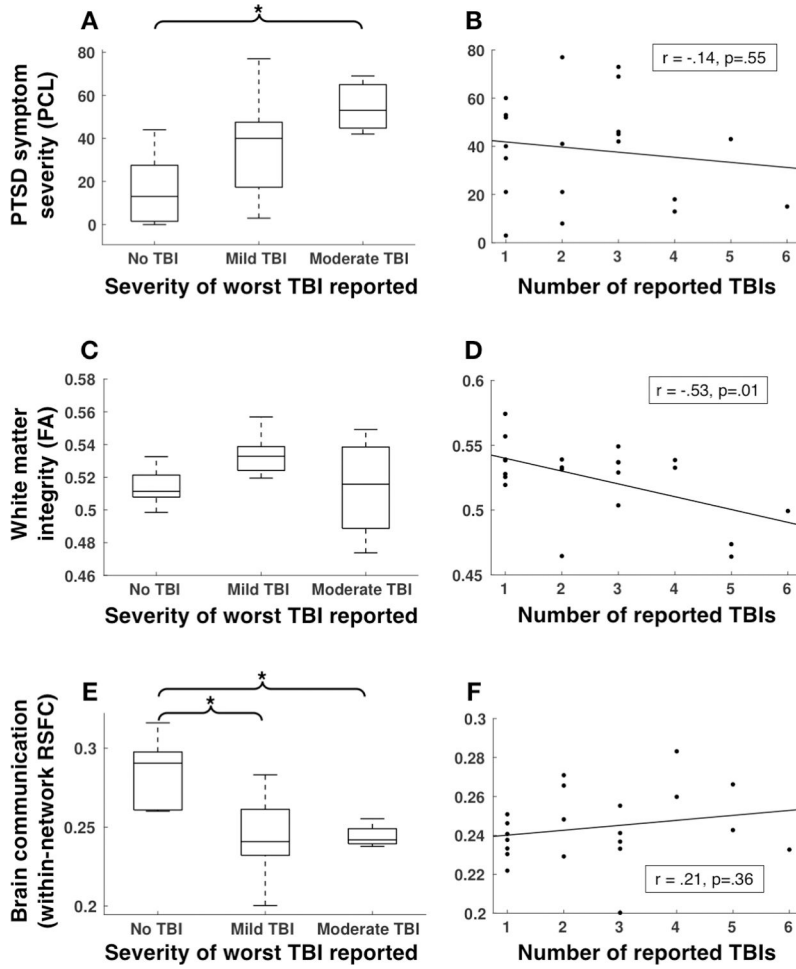


Figure 4: Relationships between TBI status / number and PCL-5, FA, and RSFC.
A,C,E: ANOVAs tested whether PCL-5 scores (A), whole-brain FA (C), or whole-brain RSFC (E) differed between groups who had suffered no TBIs, at least one mild TBI, or at least one moderate TBI. * indicates significant ($p < .05$) post-hoc pairwise differences identified after observing a significant main effect of TBI status. **B,D,F:** Correlations tested whether the total number of TBIs suffered (in individuals with at least one TBI) was associated with PCL-5 scores (B), whole-brain FA (D), or whole-brain RSFC (F).

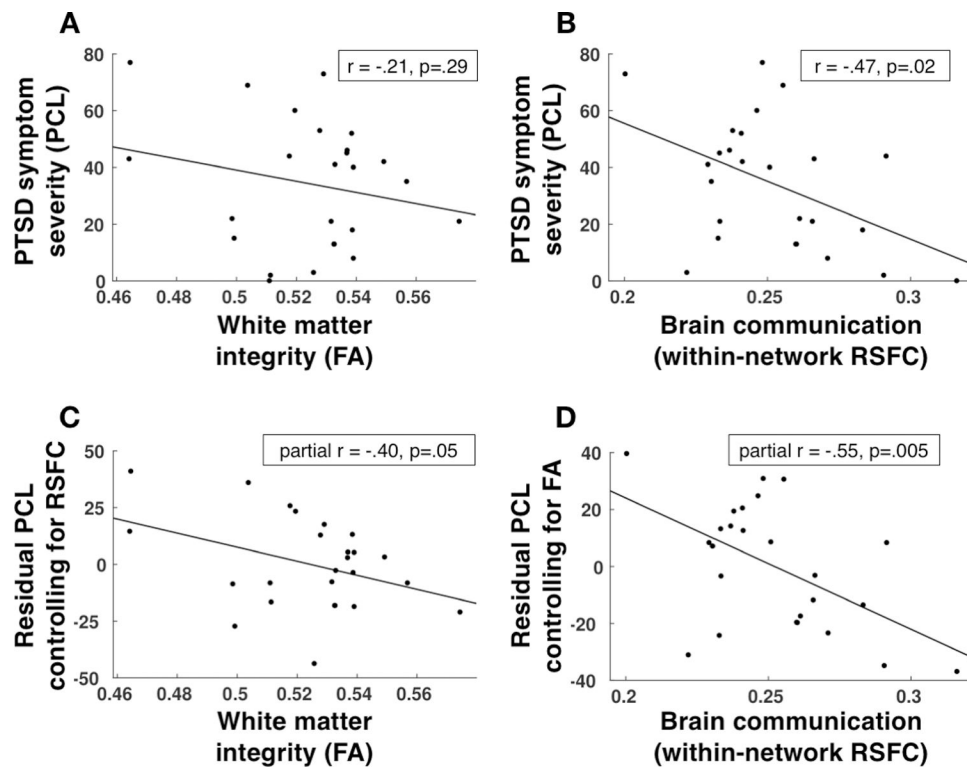


Figure 5: Relationships between FA/ RSFC and PCL-5 scores.

A: Relationship between whole-brain FA and PCL-5 score. **B:** Relationship between whole-brain RSFC and PCL-5 score. **C:** Relationship between whole-brain FA and PCL-5 score after controlling for RSFC. **D:** Relationship between whole-brain RSFC and PCL-5 score after controlling for FA.

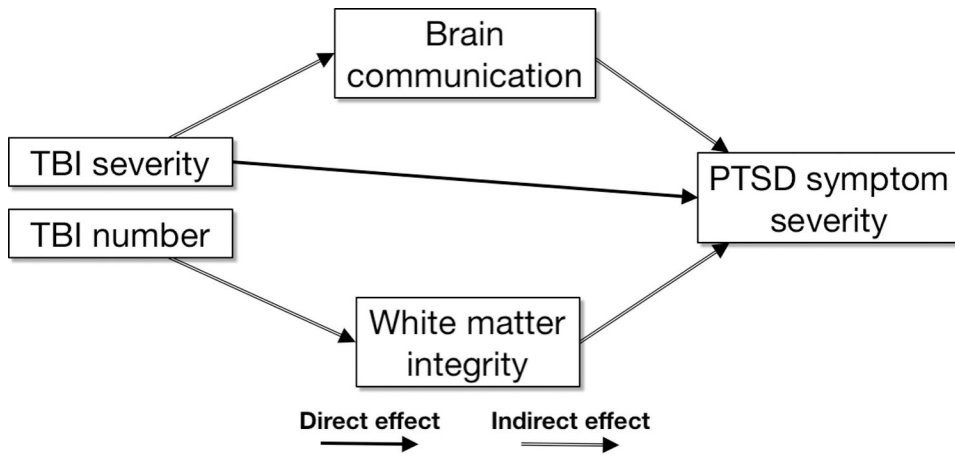


Figure 6: Observed effects for how TBI increases risk for PTSD symptoms by altering brain structure and function.

We observed two separate pathways by which separable aspects of TBI influence PTSD severity. A direct effect (solid line) of TBI on PTSD severity was observed for TBI status but not number. This effect was mediated by an indirect effect of TBI on brain communication (RSFC). A separate indirect effect of TBI number was observed on white matter integrity (FA), which was independently related to PTSD severity after controlling for brain communication.

Table 1:
Demographic and assessment measures in each TBI group.

The “Test” column shows the p value from a statistical test of differences between groups. This p value is variously derived from a Chi-square test (Gender, # with PTSD diagnosis, # on medications), a one-way ANOVA (Age, fMRI data retained, % fMRI data lost, PCL-5, FCES), or a two-sample t-test between the Mild and Moderate groups (# TBIs, Time since last TBI).

	No TBI	Mild TBI	Moderate TBI	Test
N	5	17	4	--
# F	0	3	1	p=.53
Age (years)	37.4 ± 13.3	38.2 ± 11.8	35.8 ± 14.4	p=.94
fMRI data frames retained	1848 ± 1336	2502 ± 1213	2784 ± 879	p=.46
% fMRI data lost	26.8 ± 28.4	22.7 ± 15.9	24.1 ± 15.2	p=.91
# TBIs	--	2.0 ± 1.1	3.0 ± 1.6	p=.55
Time since last TBI (years)	--	11.7 ± 10.6	7.5 ± 3.3	p=.44
Total PCL-5	16.2 ± 17.9	35.9 ± 22.0	54.7 ± 13.6	*p=.05
# with clinical PTSD diagnosis	2	7	2	p=.94
Total FCES	10.8 ± 14.5	30.6 ± 33.4	42.7 ± 7.6	p=.28
# participants on medications				
Anti-depressant	3	8	1	p=.57
Anti-psychotic	0	2	0	p=.56
Benzodiazepines	0	1	0	p=.76
Mood stabilizer	0	1	1	p=.33